Supplemental IDS

Applicants submit herewith a Supplemental IDS and a fee under CFR §1.17(p). It is respectfully requested that the publications cited in the Supplemental IDS be considered by the Examiner and made of record in this application.

Claim Rejections Under 35 USC § 103(a)

The Examiner rejects claims 1-4, 6 and 17-18 as obvious over Daub et al (Nature, 379 (1996) 557-560) in view of Bradbury et. (US 6,258,817) and Tortora et. al. (Clinical Cancer Research 7, (2001) 4156-4163). We respectfully request reconsideration of this rejection.

The present claims are directed to a composition encompassing the endothelin antagonist ZD4054 and the EGFR TKI ZD1839 (Iressa). The Examiner relies upon the disclosure of Daub et al. The Examiner correctly points out that Daub et al indicates that Endothelin-1 can transactivate EGFR. However the Examiner then suggests that:

"These statements clearly suggest the use of a combination of an endothelin antagonist and an EGFR TK inhibitor for the treatment of cancer."

This is not the case and nowhere does Daub remotely suggest that such a combination would be of any benefit in the treatment of cancer. In fact, as correctly pointed out by the Examiner, Daub et al state at the bottom of page 560, col 1 that:

"*more details of this RTK transactivation mechanism are needed to clarify its role in the regulation of biological processes and pathophysiology of diseases such as cancer"*

A person of ordinary skill in the art would see that the teaching of Daub et al. discloses that the ligand endothelin-1 can transactivate phosphorylation of the epidermal growth factor receptor (EGFR). However, as is clearly stated in the last paragraph of Daub et al. it is unclear what the mechanism of the transactivation is and whether or not this has any effect in the treatment of cancer. Accordingly, a skilled person would view the teaching in Daub et al as a finding that endothelin-1 transactivation of EGFR may have an effect in diseases such as cancer. A person of ordinary skill in the art would view such a statement as entirely speculative. Nowhere in Daub

et al is there any disclosure or suggestion of combining an endothelin receptor antagonist with an EGFR TKI.

There is nothing in the teaching of Daub et al. that would lead a skilled person to combine an endothelin receptor antagonist with an EGFR TKI or that to do so would provide any benefit. There is certainly nothing in Daub et al that would suggest the specific combination of ZD4054 and Iressa (ZD1839).

In view of the speculative nature of the teaching in Daub et al and the fact that this reference does not suggest combining any EGFR TKI with an endothelin receptor antagonist it is respectfully submitted that the Examiner has not established a prima-facie argument that the present claims are obvious over Daub et al.

The Examiner relies upon the disclosure of Bradbury et al to support his argument of obviousness. However, Bradbury et al fails to complete the deficiencies in the disclosure of Daub et al. The Examiner correctly points out that Bradbury discloses the compound ZD4054. However, this compound is one of about 70 compounds disclosed in Bradbury et al. Even in claim 3, of Bradbury relied upon by the Examiner, there are 11 different compounds and no indication that ZD4054 should be selected over and above any of the other compounds disclosed therein. Therefore, it is submitted that there is nothing in Bradbury et. al that would lead a skilled person to select the specific compound ZD4054 from the many other compounds disclosed therein. Furthermore, there is nothing in Bradbury et al to suggest that the specific compound ZD4054 is suitable for the use in the treatment of cancer.

There is certainly nothing in Bradbury et al that would lead a skilled person to combine an endothelin receptor antagonist such as ZD4054 with an EGFR TKI such as Iressa (ZD1839) in accordance with the presently claimed invention.

The Examiner also relies upon the teaching of Tortora et al. However, this reference merely discloses that Iressa (ZD1839) may be used in combination with PKAI in the treatment of

cancer. There is nothing in Tortora et al that would suggest combining Iressa with any endothelin receptor antagonist.

Even if a skilled person were to combine all of the teachings of Daub et al, Bradbury et al and Tortora, despite there being no motivation to do so, such a person would not arrive at the present invention, because none of the references suggest combining an EGFR TKI with an endothelin receptor antagonist. As discussed above, contrary to the Examiner's position, there is no teaching in Daub that would suggest such a combination and the other references relied upon by the Examiner, Bradbury et al and Tortora et al also fail to suggest such a combination.

In order for a skilled person to arrive at the specific combination of ZD4054 and Iressa starting from the teaching of Daub, Bradbury and Tortora et al, the skilled person would need to take the following steps:

- Decide to combine an EGFR TKI with an endothelin receptor antagonist, despite there being no suggestion to do so in Daub et al and despite the clear teaching in Daub that the relevance of endothelin induced transactivation of EGFR in cancer is not clear;
- specifically select the compound ZD4054 from the many known endothelin receptor antagonists in the prior art, despite there being no indication in the prior art that this compound would be effective in the treatment of cancer;
- specifically select Iressa from the many known EGFR TKIs in the prior art; and finally
- decide to test the specific combination of ZD4054 and Iressa for activity against cancer, despite none of the cited prior art even remotely suggesting that such a combination would have any benefit.

It is submitted that a person of ordinary skill in the art would not find such steps to be obvious in view of the sited references. It is respectfully submitted that any suggestion the present claims are obvious is based upon an impermissible hindsight analysis starting from the presently claimed invention. Such a hindsight benefit was not available to the inventors when the present invention was made. Based upon the cited prior art it is respectfully submitted that the presently claimed invention is not obvious.

In further support of the present invention the Examiner is asked to consider the publication of Rosano et al., Cancer Research (2007), 67(13), p. 6351-6359 submitted herewith on a Supplemental IDS.

Rosano et al describes the results of a research program that was sponsored in part by the assignee of the present application, AstraZeneca. Rosano et al studied the effect of the combination of Iressa and ZD4054 in HEY and OVCA 433 ovarian cancer cells. Rosano et al found that in HEY cancer cell *in-vivo* xenograft models, a combination of ZD4055 and Iressa resulted in a statistically significant reduction ($p<0.001$) in the time course of tumour growth compared to the use of either ZD4054 alone or Iressa alone (see Rosano et al page 6356 col 1, figure 5 (page 6357) and Table 1 (page 6358). Furthermore, Rosano et al state (p 6356, col 1):

"the combined treatment was highly effective with no hisolological evidence of HEY tumours in 4 out of 10 mice"

The beneficial effects of the combination of ZD4054 and the EGFR TKI Iressa could not have been predicted based upon the cited prior art. As discussed above there is nothing in the cited art that would lead a skilled person to combine an endothelin receptor antagonist with an EGFR TKI with any expectation of success. There is certainly nothing in the art that would lead a skilled person to expect that such a combination would provide unexpected benefits as illustrated by the Rosano et al publication.

It is therefore respectfully submitted that the present claims are not obvious in view of the cited references, either alone or in combination, and Applicants request that the Examiner reconsider and withdraw this rejection.

Claim Rejections Under 35 USC § 112, First Paragraph

The Examiner suggests that claims 7, 10, 13-16, 19 and 21-24 are not supported by information in the description that would enable a skilled person to make or use the invention. It is submitted that a skilled person would have no difficulty in using the claimed invention based upon the information disclosed in the present application. The description contains extensive teachings on suitable examples of both endothelin receptor antagonists and EGFR TKIs. The description also gives guidance on suitable dosage forms and cancers where the claimed combination may be effective. The examples in the present application illustrate that the EGF stimulates the same proliferative and survival pathways as endothelin-1 and may therefore be useful in the treatment of osteoblastic bone metastases associated with a number of cancers.

Further support for the presently claimed combinations is provided by the data published by Rosano et al discussed above and submitted herewith in a Supplemental IDS. This clearly shows that the combination of ZD4054 and Iressa is effective in a xenograft model using ovarian cancer cells. In view of the disclosure in the application together with the additional supporting data in Rosano et al. it is respectfully submitted that a skilled person would be able to use the claimed invention without undue experimental effort. The Examiner is therefore requested to withdraw this objection.

A petition for a one-month extension of time is being filed herewith. The Commissioner is hereby authorized to charge the fee for a one-month extension of time to deposit account No. 50-3231, referencing Attorney Docket No. 100864-1P US.

Although Applicants believe no additional fees are due, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. 100864-1P US.

Respectfully submitted,

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